VACCINE THERAPY IN INFECTIOUS BRONCHITIS AND ASTHMA*

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DISCUSSION *by Albert H. Rowe, M. D., Oakland; George Piness, M. D., Los Angeles.*

IN two previous papers [1] the authors attempted to classify nontuberculous cough according to its underlying pathology. Based upon a study of two hundred cases selected from routine clinic and private practice, twenty different causes were found. The two prevailing groups, a 38 per cent "undiagnosed group," and a 37 per cent group which showed a "pulmonary infiltration and thickening with or without enlarged root glands," most often followed influenza, pneumonia, and occasionally pleurisy with effusion.

PREPARATION OF VACCINE

In 1919 I. Chandler Walker [2 3] pointed out the significance of vaccines in the treatment of bronchial asthma. In his early work he recognized two distinct types of asthmatic patients—those in which some foreign protein, either of the inhalant or ingestive variety, inaugurated the attack, and a second type in which the attack was aggravated or precipitated by a superimposed bacterial infection.

Since the inception of our work on infectious bronchitis and asthma, we have modified somewhat the Chandler Walker technique preparation of vaccines and of dosage, and give herewith a brief résumé of our method of preparing cultures and vaccines including our more recent modifications.

Throughout this work the following bacteriological technique was used: After thorough antisepsis of the mouth, sputum was collected daily for three consecutive days in sterile sputum jars. Thick masses of sputum, raised during an asthmatic attack or during a severe paroxysm of coughing, which usually occurred in the morning, were washed in sterile sodium chlorid solution and shaken in five cubic centimeters of plain bouillon or glucose veal broth of proper hydrogen ion concentration. Tubes of melted plain agar, to which 0.5 cubic centimeters of sterile defibrinated human blood was added, were inoculated with varying amounts of the broth emulsion of sputum and poured into Petri dishes and incubated for thirty-six hours. The various types of colonies were then picked off, subcultivated in dextrose bouillon and incubated for about twenty-four hours. The organisms from this dextrose bouillon growth were stained by Gram's method and a bile solubility test was made. Those organisms which proved to be Gram-negative cocci in chains, noncapsulated and bile insoluble were inoculated, according to the method of Hiss, into litmus waters which contained salicin, mannite, and lactose. These serum waters were incubated for fourteen days unless coagulation took place before that time. At the end of fourteen days the tubes in which change had not taken place were carefully examined according to Holman's method of classification. Vaccines were prepared in the strength of one billion organisms per cubic centimeter, the initial dose in adults being 0.05 cubic centimeter, gradually increasing by 0.05 cubic centimeter at a three to five to seven-day interval, this time being governed by the resistance of the patient, as determined by local reaction and constitutional symptoms.

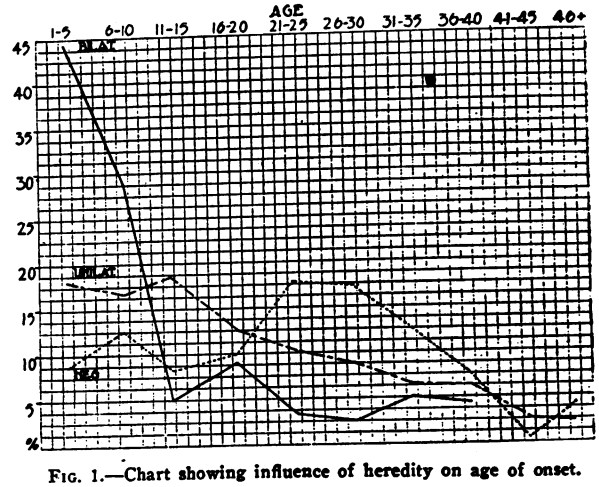

FIG. 1.—Chart showing influence of heredity on age of onset.

HEREDITY AS A CAUSATIVE FACTOR IN ASTHMA

Cooke,[4] in 1925, after a careful survey of the nature of the inheritance in asthma and preasthmatic conditions, made a graphic chart showing the influence of heredity on the age of onset. (See Fig. 1.)

Where both father and mother showed some hypersensitiveness 75 per cent of the offspring showed clinical signs before the tenth year; where there is a unilateral heredity, 35 per cent showed symptoms before the tenth year. In the third class, where there is a negative heredity history, 17 per cent showed symptoms before the tenth year. This group comprises the infectious type, and a study of the curve reveals a small peak rising from the first to the tenth year, a fall

TABLE No. 1.—*Results of Vaccines in Infectious Bronchitis and Asthma*

CASE NO.	AGE	SEX	DURATION	CLINICAL DIAGNOSIS	X-RAY FINDINGS	SPUTUM CULTURE	TYPE OF VACCINE	ETIOLOGY	RESULT VACCINE
2	56	FEMALE	31 YEARS	PULMONARY FIBROSIS & BRONCHIAL ASTHMA	PLEURAL THICKENING APICAL FIBROSIS ENLARGED ROOT GLANDS	STREP HEMOL ALPHA " BETA " VIRIDANS	AUTOGENOUS	CHRONIC BRONCHITIS	UNIMPROVED
4	46	MALE	12 YEARS	CHRONIC BRONCHITIS & ACUTE ASTHMA	PULMARY FIBROSIS BASAL CONGESTION	STREP VIRIDANS " HEMOL BETA " NON HEMOL	AUTOGENOUS	CHRONIC BRONCHITIS	IMPROVED
15	62	FEMALE	11 YEARS	INFECTIOUS BRONCHITIS & BRONCHIAL ASTHMA	ENLARGED ROOT GLANDS MARKED BASAL PERIBRONCHIAL	STAPH ALBUS STREP HEMOL ALPHA " NON HEMOL	AUTOGENOUS	REPEATED COLDS	IMPROVED
23	65	FEMALE	6 YEARS	CHRONIC MYOCARDITIS BRONCHITIS & ASTHMA	COARSE MOTTLING CALCIFICATION AT HILUS PERIBRONCHIAL THICKENING	STREP VIRIDANS " HEMOL BETA " NON HEMOL	AUTOGENOUS	REPEATED COLDS	UNIMPROVED
25	44	FEMALE	1 YEAR	INFECTIOUS BRONCHITIS & ASTHMA	ENLARGED ROOT GLANDS PERIBRONCHIAL THICKENING	STREP NON HEMOL MICR CATARRHALIS PNEUMOCOCCUS	AUTOGENOUS	INFLUENZA	WELL
30	16	MALE	2 YEARS	INFECTIOUS BRONCHITIS & ASTHMA	INCREASED BRONCHIAL MARKINGS ROOT HILUS	STREP VIRIDANS " NON HEMOL " HEMOL BETA	AUTOGENOUS	REPEATED COLDS	WELL
39	43	MALE	18 YEARS	INFECTIOUS BRONCHITIS & ASTHMA	ENLARGED BRONCHIAL ROOT GLANDS	STREP HEMOL ALPHA " BETA " VIRIDANS	AUTOGENOUS	INFLUENZA	IMPROVED
45	41	MALE	12 YEARS	PRN+SINUSITIS & BRONCHIAL ASTHMA	ENLARGED ROOT GLANDS PERIBRONCHIAL THICKENING DIAPHRAGM ADHESIONS	STAPH ALBUS STREP HEMOL BETA " VIRIDANS	AUTOGENOUS	REPEATED COLDS SINUSITIS	UNIMPROVED
55	7	MALE	5 YEARS	INFECTED ANTRA & BRONCHIAL ASTHMA	ENLARGED HILO GLANDS MARKED PERIBRONCHIAL THICKENING	GRAM NEG BACILLUS STREP NON HEMOL	AUTOGENOUS	INFLUENZAL BRONCHO PNEUMONIA WHOOPING COUGH	IMPROVED
62	28	FEMALE	6 YEARS	SINUSITIS BRONCHITIS & ASTHMA	PULMONARY FIBROSIS BASAL MOTTLING	STAPH ALBUS	AUTOGENOUS	INFLUENZAL PNEUMONIA & PLEURISY	WELL
66	35	FEMALE	9 MONTHS	POST-INFLUENZAL BRONCHITIS & ASTHMA	PLEURISY & EFFUSION FOLLOWED BY BASAL PERIBRONCHIAL	STREP HEMOL BETA " VIRIDANS	AUTOGENOUS	INFLUENZAL PNEUMONIA & EFFUSION	IMPROVED

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from the tenth to the fifteenth year, and a rapid rise to the twenty-first year, where the incidence of asthma stays at a maximal level until over thirty years, to drop gradually to the age of forty when it climbs again, reaching its maximum at the sixty-fifth year. Asthma developing after the thirteenth year, and especially after the fortieth, is usually the result of chronic foci of infection in the bronchi, tonsils, teeth, and sinuses. Here, too, development is gradual. Cough and wheezing and frequent attacks of bronchitis may go on for years before the true dyspnea of asthma begins. Many of the cases of chronic bronchitis with emphysema are truly infectious asthma and should early be recognized, because the results obtained with some of these long-standing cases warrant the belief that much better results could be obtained had they been treated along the same lines that we now follow after they have become definitely asthmatic.

CLASSIFICATION OF CASES TREATED

This present paper consists of a critical review of 481 cases reporting for routine chest examination and includes a series of 110 cases of proved tuberculosis, as checked by physical examination, x-ray films of chest, sputum, and guinea-pig inoculation for tubercle bacilli. These tuberculous cases have been eliminated from this study. Of the remaining 371 nontuberculous cases, we have been able to isolate sixty-six cases of infectious bronchitis and asthma which have received vaccine therapy, and it is this latter series that we report here in detail, giving our observations since 1920.

REVIEW OF SIXTY-SIX CASES OF INFECTIOUS BRONCHITIS AND ASTHMA TREATED WITH VACCINE

All patients treated had a history of some acute pulmonary infection, principally influenza-pneumonia, repeated colds, and in children whooping-cough was an underlying factor. All proved cases of tuberculosis have naturally been eliminated although we have in a few instances seen chronic tuberculosis, complicated with asthma, improve under an autogenous vaccine, which improvement we interpret as resulting from a tuberculin made of the patients' own sputum. (See Table No. 1.)

We have excluded from this study true bronchial asthma of the hereditary type and those cases due to pollen or protein sensitization; in the earlier years of our work, by using the scratch method of Schloss [5] with dried proteins, but in the last two years using the protein extracts of all the inhalants, danders, house dust and protein antigens by the intradermal technique of Coca and Cooke [6 7] of the Cornell Clinic. Neither a reflex asthma nor intrinsic asthma are included in this study. Intrinsic asthma is the result of infectious processes in other parts of the body, such as asthma related to and relieved by removal of an infected gall bladder or kidney or associated with the menstrual cycle.

In our classification we demonstrated that infected sinuses were responsible for 8 per cent of all chronic coughs. We therefore emphatically recommend in all bronchitis and asthma following an acute upper respiratory infection that all sinuses be thoroughly examined, drained if necessary, and a vaccine from the sinus pus or secretion be administered. In our experience we have often seen good results from the latter procedure, and have seldom seen permanent relief from a purely operative correction. How often, after submitting the patient to trying sinus operations—either drainage or the more radical method—have we seen a recurrence of all symptoms or a very temporary relief. We believe frankly that many sinus infections are true secondary infections superimposed upon a sensitive membrane; and we advocate the elimination of every condition of hypersensitiveness or allergic sensitiveness (proved such by protein skin-testing with dust, pollens, danders, and foods) by a period of rest and vaccine therapy before surgery is employed.

A detailed analysis of the sixty-six cases of infectious bronchitis and asthma reveals the following:*

Fifteen, or 22.7 per cent, we classify as "well," by which we mean the patient has been clinically relieved of all evidence of the acute paroxysms of wheezing with signs of bronchospasm for a period of over two years. We avoid the term "cured" as we feel that, in the future, repeated epidemics of influenza or other acute respiratory diseases may so alter the bacterial flora of the patient as to break down the resistance established and possibly precipitate an asthmatic attack.

Twenty-seven, or 40.9 per cent, are considered as "improved," by which we mean the patient has been relieved for over a period of six months of the real asthmatic paroxysms, has lost the associated cough and dyspnea on exertion, and is able

* The table showing the results of vaccine treatment in infectious bronchitis and asthma will appear in the reprints of this article, which may be had on application to the authors.

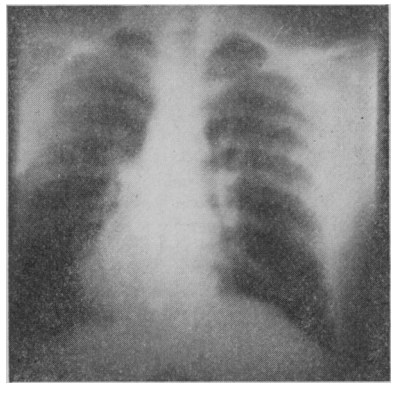

Fig. 2.—Infectious bronchitis following influenza. Marked thickening of both hila with dilatation of bronchial tubes. Marked improvement under vaccine.

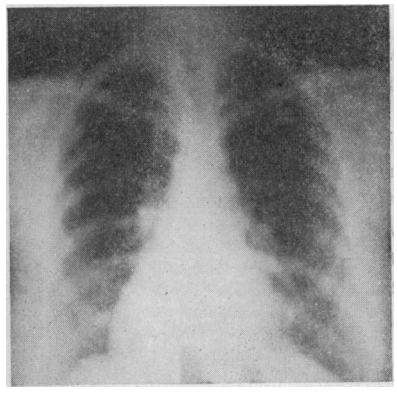

Fig. 3.—Bronchial gland involvement. History of influenza with subsequent bronchitis and asthma. Patient well after three years.

to return to his routine of living.

The remaining twenty-four, or 36.4 per cent, we have considered as "unimproved," in that they still have their nightly paroxysms of dyspnea with severe morning cough, produce large quantities of a watery, frothy sputum and, clinically, present signs of bronchospasm in their chests.

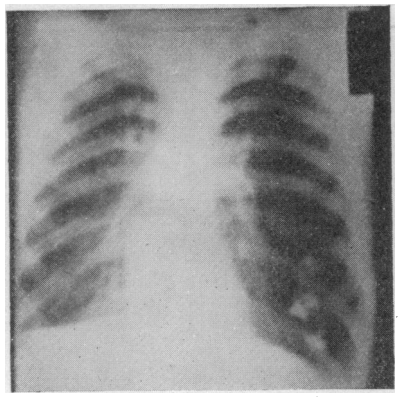

Fig. 4.—Marked thickening of both hila. Thickened pleura at both apices. Lipiodol present after two years. Marked improvement under vaccine.

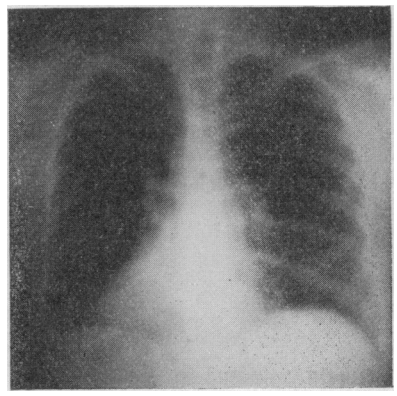

Fig. 5.—Pleural thickening at left base following pleurisy with effusion. Bronchitic and asthmatic symptoms improved under vaccine.

The combined group of well and improved patients comprise, in our small series of sixty-six cases, 63.6 per cent, and from this we conclude that vaccine therapy affords a valuable aid to our armamentarium for combating the infectious type of bronchitis and asthma. A review of the cases presented will show that our results have been almost directly in proportion to the age at onset and duration of the illness, and we feel that the earlier specific vaccine therapy is instituted the more beneficial results can be anticipated. We find further that of these cases that have responded so well that a recent history of repeated colds, sinusitis, influenza, bronchopneumonia, and whooping-cough have been the chief etiological factors.

In the group of 36.4 per cent that are "unimproved" we find, from our study of the physical and x-ray findings, that the poor results are the results of structural changes in the lung parenchyma such as pleural thickening, fibrosis, basal infiltration and bronchiectasis, or an associated myocardial lesion. It is self-evident that all infectious bronchitis and asthma had a start perhaps with an enlarged hilus gland, perhaps with peribronchial thickening, or even with mild extension into the lung parenchyma. This pathology must be discovered early if we are to effect cures and prevent chronic bronchitis, asthma, bronchiectasis, or even tuberculosis. We believe that this can be done and that our studies and results will encourage others to adopt the method of careful investigation of cough of over six weeks' duration by physical, bacteriologic, and x-ray examinations.

Our roentgenograms, a few of which have been inserted as illustrations, demonstrate clearly how cases with lung parenchyma involvement can be differentiated from those without. Pictures 2, 3, 4, and 5 are examples of types which did well under vaccine therapy. Pictures 6 and 7 are illustrative of types which did not do well and show considerable involvement of lung parenchyma.

A review of the cultural studies, as previously reported in this group of infectious asthma, shows the prevailing organisms to be: *Micrococcus catarrhalis, Streptococcus nonhemolyticus, Streptococcus hemolyticus alpha* and *beta, Streptococcus viridans,* and secondary invaders such as Gram-positive diplococci, staphylococci, and pneumococci.

In a series of twenty-two cases where we were unable to trace the onset of the asthmatic paroxysms to a specific infectious process, such as influenza, pneumonia, or whooping-cough, we resorted to the use of the ordinary stock respiratory vaccine and found that our percentages of results were:

Well—Seven cases, or 32 per cent.

Improved—Eight cases, or 36 per cent.

Unimproved—Seven cases, or 32 per cent.

These figures run parallel to our results with autogenous vaccines, and are in agreement with the work of Rackemann,[8] who does not claim specificity for autogenous vaccines. We are convinced that vaccines help in almost two-thirds of the infectious bronchitis and asthma cases, and cannot yet be sure from a culture of the sputum which cases will benefit and which will not. We do not even claim that many of our "good results"

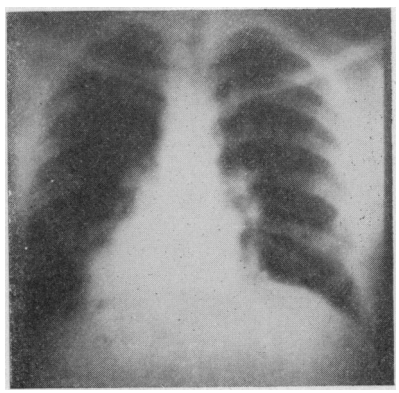

Fig. 6.—Asthma with cardiac enlargement. This type does not do well under vaccine.

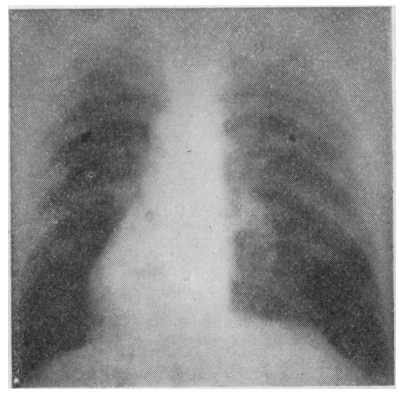

Fig. 7.—Infiltration at right hilus spreading into lung parenchyma. This type does not improve under vaccine.

may not have been just as good under rest without a vaccine. We give our results for what they are worth, believing firmly that many patients whose asthma or bronchitis is of the infectious variety can be aided by vaccine therapy and thus prevented from becoming hopeless chronic types.

CONCLUSIONS

In a study of 481 cases of chronic cough of over six weeks' duration we were able to segregate sixty-six cases of infectious bronchitis and asthma that had received vaccine therapy. In our sixty-six cases receiving vaccine therapy we classify 63.6 per cent as well and improved, and 36.4 per cent as unimproved.

A series of twenty-two cases treated with stock respiratory vaccine give parallel results, so that we do not claim specificity of autogenous vaccines.

Cultural studies to date do not inform us which cases will do well; we are influenced by the duration of the illness, age of onset, and history of repeated colds, influenza, pneumonia, and whooping-cough.

We believe that two-thirds of the cases of infectious bronchitis and asthma are amenable to vaccine therapy and that failure is the result of structural changes in the lung parenchyma or an associated myocardial lesion.

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DISCUSSION

ALBERT H. ROWE, M. D. (242 Moss Avenue, Oakland).—The paper of Doctors Voorsanger and Firestone is of great interest. It serves to emphasize two things: First, that bacterial allergy exists in a certain number of cases of asthma. Second, that nonspecific protein therapy by the use of vaccines produces in some asthmatics a nonspecific desensitization.

I feel that certain cases in their series probably are sensitive to some antigens which have not been demonstrated by the writers. During the last two years I have emphasized in several articles the fact that food allergy exists in at least 50 per cent of all food-sensitive patients without skin reactions. Alexander, using the intradermal test, is of the same opinion. A smaller percentage of pollen- and animal-emanation-sensitive patients have negative skin reactions, and with these facts in mind and an emphasis on the clinical history, and the use of my elimination diets and environmental control for diagnosis, I have found that many cases formerly classified as nonsensitive and probably due to bacterial allergy have food or other types of specific sensitization. Such cases are helped by nonspecific treatment, as witnessed by peptone therapy in England and France, but the results are certainly not as satisfactory or permanent as when the specific sensitization is found.

However, I feel there are a moderate number of bacterial-sensitive asthmatics, and the writers have undoubtedly seen more of these patients than are seen in the usual allergic clinic. Bacterial allergy, in my experience, is very uncommon in children and young adults. Superimposed sinusitis and bronchitis is not infrequent. The clearing up of sinus infection by surgery at times in nonsensitive patients is necessary, but I agree with Doctor Firestone that vaccine therapy should precede and follow such surgery to build up immunity or produce desensitization. The use of sputum filtrates made according to Wilmer's technique has been of value in a few cases in my work, and the use of vaccines in pure cultures which give local reactions with intradermal testing is to be recommended. The use of x-ray therapy, as recommended by various men, has been given a definite trial in my clinic without satisfactory results, and there is no justification for it where specific sensitization can be demonstrated.

GEORGE PINESS, M. D. (1136 West Sixth Street, Los Angeles).—Since the influenza epidemic of 1918 it has been our privilege to see a great many cases similar to those described by the essayists today. It is apparently a very common sequela to influenza and other acute infectious diseases such as pneumonia, tuberculosis, and similar conditions. It is very interesting to note, too, that the ages of most of the patients studied by the doctors were in the fourth decade of life although there is a small percentage of very young individuals in the first decade of life which is rather unusual in that it is uncommon to see infectious or bacterial types of bronchial asthma in young individuals. However, apparently there is an infectious history beyond each one of these cases.

There are several rather interesting points I wish to emphasize. The first is that apparently each and every one of these individuals was of a bacterial type because, first, they were tested to proteins of all groups and found nonsensitive; second, the characteristic history of each prior to the onset of the present condition; and third, the cases were studied so thoroughly as to eliminate any possibility of their being of an allergic type.

I noted with interest the results of treatment with autogenous and mixed stock respiratory vaccine in that it was comparative with the results of other workers. In our own work we noted that one could obtain equally as good results with the stock respiratory vaccine as with the autogenous.

The results of treatment of these cases are interesting, and the percentage of results is greater than seen in the average clinic. We are not in accord with the writers that at least 70 per cent of the cases of infectious bronchitis and asthma are amenable to vaccine therapy, but do agree with them that the failures are the result of subsequent changes in the lung parenchyma.

I do not agree with Doctor Rowe in his discussion that there are, perhaps, in among this group a number of food allergy individuals, as the histories are so clear-cut and the symptoms so definite and the findings so typical of a nonallergic infectious bronchitis and bronchial asthma.

DOCTOR VOORSANGER (Closing).—Answering Doctor Rowe, we wish to state that our present study deals with bacterial-sensitive asthmatics and does not mention the large group sensitive to proteins and foods. We grant the existence of food allergy, but are not discussing it in this paper; in fact we thought our procedure, which was most careful and painstaking, excluded this group.

Doctor Piness has very clearly stressed our main point, that in most of our cases there is a previous infectious history. He states, however, that he is not "in accord with the writers, that at least 70 per cent of the cases of infectious bronchitis and asthma are

amenable to vaccine therapy, etc." Our statement gave 22.7 per cent as well and 40.9 per cent as improved, a total of 63.6 per cent, which we feel are amenable to a vaccine. This means that the larger number, although improved, still have symptoms.

In the main we must all agree that the careful observation of asthmatic and bronchitic symptoms following any acute infection is important to prevent, if possible, changes in the lung parenchyma. If we can treat these patients early, before such changes take place, we may do much toward preventing chronic pulmonary disease.

THE LURE OF MEDICAL HISTORY

WILLIAM CHARLES WELLS

By WILLIAM DOCK, M. D.
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THE men who contributed to the rapid advance of science in the late seventeenth and early eighteenth centuries are notable for their versatility and the broad scope of their interests. John Hunter, Franklin, Lavoisier, Rumford, and Thomas Young, each showed capacity in various fields. William Charles Wells was such a searcher for facts, whose studies covered a multitude of subjects, but his cross-grained personality and his failure to make known his findings reduced their value and eclipsed his worth.

Wells was born in South Carolina in 1757, but his parents were Scotch and his education, from the ages of eleven to fifteen, and eighteen to twenty-one, was in Dumfries and Edinburgh. He spent the three years between these dates working for a Charleston physician, and after completing his Edinburgh studies stopped a short time in London, listening to William Hunter, then went as an army surgeon to Holland, where his quarrels with superiors soon led to his resignation. At Leyden he worked on his thesis, *De Frigore,* and after receiving his Edinburgh M.D. he returned to Charleston in 1780. His Tory family soon fled to Florida, where he ran the paper, was captain of volunteers, actor and theatrical manager for the plays to amuse his fellow refugees. With return of peace he went to Charleston, only to be jailed for three months in a civil suit, and again he left for Florida, then Paris, and finally, in 1785, he started to practice in London.

He records that his debts, seven hundred and fifty dollars when he began practice, increased to three thousand dollars in ten years. For several years he scarcely received a fee, but after ten years in practice he was collecting twelve hundred dollars a year, and was able, gradually, to pay off all his debts, although his income never rose over twenty-two hundred dollars. Through this time his life was austere and his circle of friends, though distinguished, was limited to five men. Of these Matthew Baillie, the greatest physician of the time, was one of the warmest. In 1812 Wells developed "hydrothorax," the condition which we now recognize as auricular fibrillation, and from this he suffered until his death in 1817. He remarked of himself, "By principle a constitutional Tory, but my manners, I should think, would lead most persons to regard me a republican."

Wells early entered the Royal Society, but even the sponsorship of Pitcairn and Baillie was inadequate to make him a Fellow of the Royal College of Physicians. The college banned any who had ever worked as apothecaries, general practitioners, or accoucheurs, and was sadly political in its organization. Wells protested against its abuses in a letter to Lord Kenyon, and later, when Baillie again urged him to accept a Fellowship, he declined. The college, founded in 1518, required its fellows to be "profound, sad, discreet, groundedly learned, and deeply studied in physic." Wells had all the qualifications except the third.

Wells' most widely known work, and one which was reprinted often and included in many medical texts, was his "Essay on Dew," which was awarded the Rumford medal. From observations made in his own garden with crude instruments, he had correctly evaluated the importance of radiation of heat from the objects on which dew condensed, and established the facts of dew formation. His essay was curtly dismissed by Thomas Young in the *Quarterly Review,* and this added another source of sorrow to the unhappy invalid who had carried out his studies on dew in spite of his ill health. His first studies on vision were published in 1792, and he continued his interest in this subject, making important observations on the optical axis, convergence, pupillary changes during accommodation, and on the effect of belladonna on the pupils and on accommodation. He described a case of total alopecia, and one of chloasma. In connection with the latter he made some observations on the immunity of negroes to certain diseases, and to the analogy between the improvement of domestic animals by selection and the development of varieties of man by a similar mechanism of nature. What was done for animals artificially "seems to be done with equal efficiency though more slowly, by nature, in the formation of varieties of mankind, fitted for the country which they inhabit. Of the accidental varieties of man, which would occur among the first scattered inhabitants, some one would be better fitted than the others to bear the diseases of the country. This race would multiply, while the others would decrease, and as the darkest would be the best fitted for the (African) climate, at length become the most prevalent, if not the only race." Darwin regarded this observation of Wells' as the "first recognition of the principle of natural selection."

Of the case reports made by Wells those on the infectiousness of erysipelas, on unusual complications of thoracic aneurysm, and one on epilepsy and hemiplegia due to a traumatic cranial lesion, and improved by removal of a button of bone with a spike projecting into the dura, are of some interest. His most important medical contributions concern rheumatic endocarditis and dropsy. He recorded several cases illustrating the relation between rheumatic fever and heart disease, a fact previously noted by Pitcairn and